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# CCDR

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## Inside this issue: Vector-borne diseases in Canada

In this issue, we explore infectious diseases in Canada that are spread by mosquitoes, deer mice and ticks. The good news is that number of reported cases of West Nile virus has been decreasing for the past 10 years. However, other vector-borne diseases are on the rise. Two bunyaviruses in Canada can cause a West Nile virus-like illness – and there is evidence to suggest they have been under-diagnosed. Another bunyavirus is hantavirus that is spread by deer mice and can cause a severe respiratory illness. Read the first national human surveillance report on Lyme disease since it became notifiable in Canada in 2009. Given the incidence of these vector-borne diseases in Canada, there is ample reason to promote personal protection during outside activities this summer!

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### Useful link

Public Health Agency of Canada. **West Nile Virus and Other Mosquito-borne Disease National Surveillance Report. 2014** http://www.phac-aspc.gc.ca/wnv-vwn/nsr-rns_2014/final/index-eng.php

### Upcoming webinar

**June 18, 2015:** Public Health Agency of Canada. **Chlamydia among young women: A resource for population-specific information**.
https://gts-ee.webex.com/gts-ee/onstage/g.php?MTID=e0c9b9492cea1eaf1948f210e1d6ea5af

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Canada

# Emerging mosquito-borne bunyaviruses in Canada

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## Abstract

California serogroup and Cache Valley viruses are arboviruses (tick- and mosquito-borne pathogens) belonging to the genus *Orthobunyavirus* (Family Bunyaviridae). Although the majority of exposures to these viruses result in asymptomatic or mild infections, both California serogroup and Cache Valley viruses can cause febrile and neurological diseases similar in nature to those associated with infections by West Nile virus. California serogroup and Cache Valley viruses are widely distributed across North America and circulate in a number of vertebrate hosts and mosquito vectors, including several species of *Aedes* and other non-*Culex* mosquitoes. The Jamestown Canyon and snowshoe hare viruses are the most common kind of California serogroup viruses found in Canada and have been identified throughout the country. These potential pathogens may be contributing to a higher burden of illness than previously recognized and should be considered as part of the differential diagnosis for febrile and neuroinvasive disease during the mosquito season. Diagnosis can be made by requesting a diagnostic panel at the Viral Zoonoses program at the National Microbiology Laboratory. To decrease the risk of infection, education about these viruses and the importance of personal preventive measures is warranted.

## Introduction

The Bunyaviridae family of RNA viruses is a very large, diverse and globally-distributed group of viruses that infect plants, vertebrates and invertebrates (1). Many medically-important bunyaviruses are vector–borne viruses that can infect rodents or arthropods. For example, hantaviruses such as Sin Nombre virus are transmitted by deer mice and cause hantavirus pulmonary syndrome (2, 3). Arboviruses are bunyaviruses which infect and are transmitted by ticks and mosquitoes. Mosquito-borne bunyaviruses belong to the *Orthobunyavirus* genus. There are approximately 170 viruses in this genus which includes 48 species and 19 serogroups. e Within two of these serogroups there are four emerging viruses that are becoming increasingly recognized as important human and veterinary pathogens (1). (**Text table**)

**Four emerging arboviruses in North America in the *Orthobunyavirus* genus of the Bunyaviridae family**[1]

***California serogroup*:** There are 17 viruses in this serogroup including:
- California encephalitis virus
- Inkoo virus
- Jamestown Canyon virus
- La Crosse virus
- Snowshoe hare virus
- Tahyna virus

***Bunyamwera serogroup*:** There are 23 viruses in this serogroup including:
- Cache Valley virus

[1]The four emerging viruses are identified in bold

The California serogroup viruses circulate widely throughout the world. They include the Inkoo virus in Europe; the Tahyna viruses in Europe, Asia and Africa; and the La Crosse, snowshoe hare and Jamestown Canyon viruses in North America (4, 5). Several California serogroup viruses are associated with mild flu-like diseases and severe

central nervous system infections (4, 6, 7, 8). The snowshoe hare virus has been implicated in neurological cases mainly involving children (4, 8, 9). Another widespread California serogroup virus is the Jamestown Canyon virus which has been recently been identified as an emerging cause of febrile and neuroinvasive disease in Canada and the United States (6, 7, 8, 10, 11, 12). The La Crosse virus is closely related to the snowshoe hare virus and is the primary cause of viral encephalitis in children in the United States (on average 80 to 100 cases per year) and the second leading cause of arbovirus-associated neuroinvasive disease in North America (6,13). No La Crosse virus associated clinical cases have been reported yet in Canada presumably due to the limited occurrence of its vectors (e.g., *Aedes triseriatis* and *Aedes albopictus*); however, future climatic changes could influence the northern expansion of these mosquito species (14).

A fourth emerging mosquito-borne *orthobunyavirus* is the Cache Valley virus (Bunyamwera serogroup) which circulates throughout North and South America (15, 16). It has been primarily associated with disease in livestock, especially sheep (15). However, patients with undiagnosed illness in western Canada have been found to harbour Cache Valley virus-specific antibody (17, Drebot unpublished findings) and several cases of neuroinvasive disease in humans caused by Cache Valley virus have been documented in the United States (18,19).

There are no specific treatments or currently-available vaccines for the California serogroup and Cache Valley virus infections. Treatment for these viral infections typically includes supportive care and management of complications, such as relieving increased intracranial pressure.

The health impact of these bunyaviruses may be significantly greater than previously thought. From 1989 to 2005, no cases of California serogroup virus infections were documented in Canada due to the discontinuation of diagnostic procedures for identifying these pathogens. As part of an enhanced approach to further develop serological assays for West Nile virus and other mosquito-borne arboviruses, new testing methodologies have been implemented and added to the existing diagnostic panels at the Viral Zoonoses program at the National Microbiology Laboratory in Winnipeg Manitoba (11, 12, 20).

There is now sufficient evidence to indicate that when patients present with febrile and neurological disease and a history of exposure to mosquitoes, both West Nile virus and mosquito-borne bunyaviruses should be considered. In this article the ecology, epidemiology, clinical aspects, diagnostics and some recent laboratory-based surveillance data of California serogroup virus and Cache Valley virus will be discussed.

## California serogroup viruses

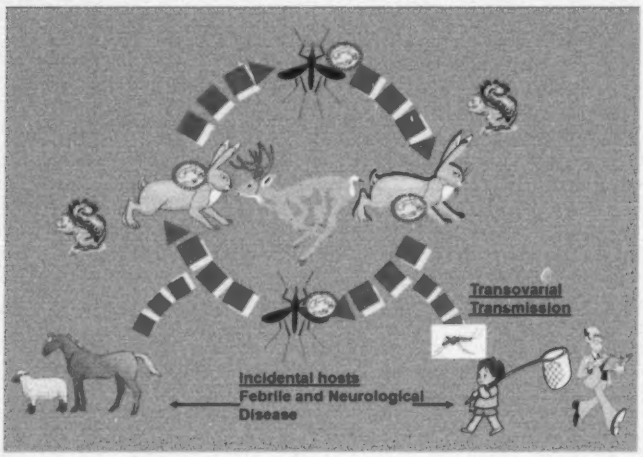
The La Crosse, snowshoe hare and Jamestown Canyon viruses are the main emerging and neglected California serogroup viruses in North America (4, 6, 7, 9, 11, 13). Humans may acquire infection through mosquito bites resulting in asymptomatic to mild febrile illness (with fever, chills, abdominal pain, cough, headache and photophobia) and acute central nervous system infection (meningitis and/or encephalitis). Although most patients with California serogroup viral encephalitis recover fully, some long-standing neurologic sequelae have been reported, in particular for the La Crosse virus (13).

In Canada, California serogroup virus activity has been demonstrated in all provinces and territories (8, 9, 11, 12). From 1978 to 1989, 23 cases of symptomatic infection were diagnosed in Canada, the majority of which were snowshoe hare viruses (18 cases) with three cases of Jamestown Canyon virus and two California serogroup viruses of unknown identity (8, Artsob and Drebot, unpublished findings).

The risk for California serogroup virus exposure extends from May to October, as the predominant vectors carrying the snowshoe hare and Jamestown Canyon viruses are (unlike West Nile virus) non-*Culex* mosquitoes such as *Aedes*, *Culiseta* and *Anopheles* species (4,7,8). As well, the amplifying hosts / reservoirs for these viruses are either small mammals such as squirrels, chipmunks, hares and various rodents (snowshoe hare viruses), or larger animals such as deer and elk (Jamestown Canyon viruses) **(Figure 1).** Livestock such as horses, cattle and sheep also exhibit significant levels of seroprevalence, however, they probably do not contribute significantly to the enzootic transmission cycle of these viruses due to low viremia (21, Drebot, unpublished findings). Transovarial transmission is the most likely overwintering mechanism which involves

infected mosquitoes transmitting virus to their offspring in the egg where the snowshoe hare and Jamestown Canyon viruses overwinter.

**Figure 1: California serogroup (Jamestown Canyon, snowshoe hare viruses) and Cache Valley virus transmission cycles**




The presence of both vectors and reservoirs throughout woodlands and parks in both rural and urban areas increases the possibility of significant levels of virus circulation not only in southern parts of Canada but also in northern locations such as the Yukon, North West Territories and Alaska. As a result, there is risk for human and animal exposures during the entire mosquito season and over a wide geographic area.

### *Snowshoe hare virus*

The snowshoe hare virus circulates widely across Canada and the United States in enzootic cycles involving non-*Culex* mosquitoes and mammals such as hares and squirrels (8). It was first isolated in 1958 from the serum of a snowshoe hare *(Lepus americanus*) in Montana. Human disease caused by this virus was initially documented in Canada in 1978 when three encephalitis infections were diagnosed in Québec (three boys aged 7, 6 and 10 years old with symptoms of fever, nausea, vomiting, headache, confusion and agitation) and one case of meningitis identified in Ontario (30 year old male) (8). Most of the snowshoe hare virus cases were associated with neuroinvasive diseases such as encephalitis and meningitis and predominately involved children, a similar epidemiology that is observed for the closely related La Crosse virus which is found in the eastern and Midwestern United States (13).

### *Jamestown Canyon virus*

The Jamestown Canyon virus was initially isolated in the United States in 1961 from a pool of *Culiseta inornata* mosquitoes collected in Jamestown Canyon near Boulder, Colorado (4). Jamestown Canyon virus infections may cause a similar range of diseases as observed for the snowshoe hare virus including both febrile and acute central nervous system infection (4, 7). Respiratory system involvement has been observed in a number of patients. In contrast to the snowshoe hare virus, most Jamestown Canyon virus-infected individuals with severe symptomatic disease are adults and their primary reservoirs appear to be deer and related ruminants (7).

The Jamestown Canyon virus was thought to be primarily concentrated in eastern North America, but recent reports have suggested that the geographic distribution of human Jamestown Canyon virus infection is wider than previously recognized (7). Based on serosurveys in Canada and the United States it is estimated that approximately 25% of the population may have antibodies to the Jamestown Canyon virus but the actual seroprevalance rates may range from 1% to 40% or greater for both the Jamestown Canyon and snowshoe hare viruses depending upon the region (22,23,24, Drebot unpublished data). The estimated ratio of asymptomatic to

symptomatic infections is believed to be in the range of 100:1 to 1500:1 based on studies involving the related La Crosse virus (25). Many human infections of the Jamestown Canyon virus may go undetected because of its nonspecific clinical presentation and limited availability of sensitive tests for the agent.

### Clinical symptoms

The most frequent symptoms include headache, fever, dizziness and vomiting, while photophobia, respiratory distress and rash are also observed (25, 26). When the central nervous system is affected, clinical syndromes ranging from febrile headache, muscle weakness to aseptic meningitis to encephalitis may occur and these are usually indistinguishable from similar syndromes caused by other viruses. California serogroup viral meningitis is characterized by fever, headache, stiff neck and pleocytosis and infections involving children may result in seizures. Snowshoe hare / Jamestown Canyon virus associated encephalitis is characterized by fever, headache and altered mental status ranging from confusion to coma with or without additional signs of brain dysfunction (7, 8, 26, 27). Severe California serogroup infections result in a variety of sequelae such as behaviour changes, learning disabilities and cognitive deficits. (25, 26)

### Laboratory diagnostics

California serogroup virus serological procedures such as the IgM enzyme-linked immunosorbent assay (ELISA) and plaque reduction neutralization test (PRNT) are the primary testing methodologies used to diagnose California serogroup infections (7, 11, 12, 13). Acute and convalescent sera from suspected cases are recommended for determining the diagnostic rise or decrease in California serogroup virus specific antibody titres and documenting seroconversions. For neurological disease cases, samples of cerebrospinal fluid should be included for detection of acute IgM antibody or viral genomic sequences (by the polymerase chain reaction) which would also constitute confirmatory laboratory evidence of an infection associated with accompanying clinical characteristics (11, 12, 26). However, it should be noted that it is quite rare to detect the snowshoe hare or Jamestown Canyon viruses in both brain biopsy tissue and the cerebrospinal fluid either by polymerase chain reaction or isolation (26).

As observed for West Nile virus infections, there is evidence that IgM may persist for several months or even years in sera from patients exposed to California serogroup viruses (27). As a result, lingering IgM may confound the diagnostics used in identifying current cases of California serogroup illness when positive serology is documented using only acute samples of sera.

**Case definitions for California serogroup viruses** (Snowshoe hare and Jamestown Canyon viruses)

A **"confirmed" case** is based on any of the following laboratory criteria:

- Fourfold or greater change in virus-specific antibody titre
- Presence of either virus-specific IgM or neutralization antibodies in cerebrospinal fluid
- Detection of virus-specific RNA in cerebrospinal fluidor isolation of virus by cell culture (rarely observed)

A **"probable" case** includes:

- An individual with a clinically compatible illness (and symptoms observed during the mosquito season) and detectable snowshoe hare / Jamestown Canyon virus IgM antibody and virus specific neutralization antibodies in the acute serum sample

### Laboratory-based surveillance

The National Microbiology Laboratory developed serological platforms to test for California serogroup virus infections using IgM ELISAs and PRNTs in 2005 following a period when there were no diagnostic procedures for identifying these pathogens (9,11). By incorporating these assays for testing suspect cases of non-West Nile virus mosquito-borne agents, the first California serogroup infection in over 15 years was identified involving a pediatric snowshoe hare virus case in Nova Scotia in 2006 (9).

Since 2006, over 200 "probable" and "confirmed" cases of snowshoe hare and Jamestown Canyon virus infections have been documented including confirmed cases of neurological disease in various provinces across Canada (11, 12; Drebot, unpublished findings). Detailed clinical and diagnostic workups and case identification involved one patient in British Columbia, three patients in Alberta, one patient in Manitoba, one patient in Québec,

one patient in New Brunswick and one patient in Nova Scotia (10, Drebot, unpublished findings). The majority of probable and confirmed cases have been associated with the Jamestown Canyon virus (70%) which is in contrast to what was previously observed in the 70 and 80's when most cases of California serogroup virus infection in Canada associated with the snowshoe hare virus (8). It is unclear whether this is due to a change in virus circulation or abundance or is due to improved sensitivity and specificity of serological diagnostics. Grimstead et al have indicated that previously-used HI assays may not have been sensitive enough to detect Jamestown Canyon virus exposures as compared to currently employed serological methods such as IgM ELISAs (24). The preponderance of the Jamestown Canyon virus in recent serosurveys is also consistent with this virus being the California serogroup agent the majority of individuals are exposed to in Canada (11,12,22,23, Drebot, unpublished findings).

## Cache Valley virus

The Cache Valley virus is another mosquito-borne *orthobunyavirus* that is also primarily transmitted by non-*Culex* mosquitoes. Similar to the Jamestown Canyon virus, its main animal reservoir / amplifying host is believed to be deer (15, 16). The Cache Valley virus was first isolated in 1956 in Cache Valley, Utah, USA but is endemic throughout Canada, the United States, the Caribbean, Mexico and Argentina (15, 28, 29). While the Cache Valley virus can infect humans as well as a wide variety of livestock, clinical disease has been primarily documented in sheep (15). Most natural infections in non-pregnant sheep are subclinical; however, the virus may cross the placenta in pregnant ewes and infect the fetus resulting in the birth of diseased lambs with malformations observed in the musculoskeletal and central nervous systems. The Cache Valley virus has been suspected in past sheep outbreaks in Canada based on positive serology among ewes in farm flocks but in 2012 and 2013, Cache Valley virus infections in livestock were verified by viral isolation and tissue positive PCR for the first time in Ontario and Québec (30,31). Seroprevalence studies have demonstrated seropositivity rates of up to 40% among sheep and other ruminants at various sites in Saskatchewan, Ontario and Québec.

### Clinical cases

Human infections with the Cache Valley virus appear to be quite common in areas where the virus is enzootic and seroprevalence rates in humans may be as high as 18% (28). Although human neuroinvasive illness has rarely been diagnosed, there have been three reports of severe Cache Valleyviral associated disease in the United States including a fatal case of encephalitis (18, 19). The low frequency of cases is presumably due to the fact that laboratories rarely test for the virus and cases involving febrile and neuroinvasive disease may be undiagnosed. Recent serological testing of West Nile virus suspect-cases from Manitoba and Saskatchewan identified Cache Valley virus exposures in 5 to 16% of patients screened for viral specific antibody (17). As well, the strain of Cache Valley virus isolated from a recent human case in the US was almost identical to the isolates obtained during the sheep outbreaks in Québec and Ontario indicating that currently circulating genotypes of the virus do exhibit the potential for pathogenicity in humans and other animals (30). The Cache Valley virus has also been associated with congenital defects in humans (i.e., macrocephaly in infants), but the specific role that this virus may play in inducing these abnormalities has not been determined and further verification is warranted (32).

### Laboratory diagnosis

There is no commercial diagnostic kit available for identifying cases of the Cache Valley virus and antibodies to the agent will not cross react significantly in California serogroup assays. The National Microbiology Laboratory conducts neutralization tests to identify Cache Valley virus-specific antibodies in sera and has viral isolation procedures in place as well (17). IgM and IgG ELISAs are currently in development for the Cache Valley virus to facilitate case detection. Given the wide ranging nature of the potential pathogen in Canada and the increasing identification of cases among livestock in the country, the potential for neuroinvasive cases among patients during the mosquito season is low but remains possible.

## Discussion

Emerging and neglected mosquito-borne bunyaviruses such as the California serogroup and Cache Valley viruses may be contributing to a significant number of cases of undiagnosed febrile and neuroinvasive disease during the Canadian mosquito season. Recent documentation of Jamestown Canyon and snowshoe hare virus cases indicate that these viruses are contributing to significant morbidity when mosquitoes are prevalent. A recent study by Kulkarni et al (33) used spatial and temporal statistics to identify seasonal clusters of Canadian hospitalizations and suggested arboviral agents in addition to West Nile virus may be implicated as undetermined aetiologies of neurological disease. It should be noted that the seasonal and geographic risk for exposure for mosquito-borne bunyaviruses is more widespread than West Nile virus.

Significant numbers of arthropod-borne bunyavirus infections are likely being undetected due to a lack of commercially-available diagnostic assays and low-level surveillance. Currently the National Microbiology Laboratory is the only laboratory in Canada to perform California serogroup virus testing. Only one commercial serological assay for California serogroup viruses exists and it is primarily used as an immunofluorescent test for La Crosse virus antibody (20). Although serological cross reactivity between the snowshoe hare, Jamestown Canyon and La Crosse viruses may occur, recent studies have shown that La Crosse virus-specific diagnostic platforms may not always detect antibodies to other California serogroup viruses and cases may be missed (20). Further development and implementation of commercial and "in house" kits for a wider variety of *orthobunyaviruses* may aid in detecting additional cases associated with these viruses. Improved and timely diagnostics will aid clinicians in making patient-care and management decisions.

Disease prevention is primarily achieved through public education. Personal risk reduction measures include decreasing the risk of mosquito bites by avoiding exposure, wearing protective clothing and using insect repellent. The elimination of mosquito breeding sites to prevent arboviral infection is also recommended.

## Conclusion

Febrile and neurologic illness may be caused by emerging mosquito-borne bunyaviruses in Canada. Clinicians should consider California serogroup and Cache Valley viral infections in the differential diagnoses when an arboviral infection is suspected and testing for West Nile virus is inconclusive. Enhanced surveillance and the utilization of a wider panel of diagnostic assays could lead to the further identification of neuroinvasive disease caused by these emerging viruses. In the meantime, education about these viruses and the importance of personal preventive measures to decrease the risk of infection are warranted.

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## Conflict of interest

None.

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# Hantavirus pulmonary syndrome in Canada: An overview of clinical features, diagnostics, epidemiology and prevention

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## Abstract

Hantavirus pulmonary syndrome is a disease caused by the inhalation of excreta from infected deer mice. In Canada, the majority of hantavirus pulmonary syndrome cases occur in the western provinces of British Columbia, Alberta, Saskatchewan and Manitoba and the primary cause of the illness is the Sin Nombre virus. Only one case of hantavirus pulmonary syndrome has been documented in eastern Canada (Québec); however, Sin Nombre virus-infected deer mice have been identified across the country. Although cases are rare (yearly case numbers range from zero to 13 and the total number of confirmed cases in Canada now total 109), the mortality rate among infected individuals is approximately 30%. The majority of cases occur in the spring and early summer indicating seasonally-associated risk factors for viral exposure. In 2013 and 2014, a substantial increase in the number of hantavirus pulmonary syndrome cases was identified; however the cause remains unclear. No antivirals or vaccines are currently available and treatment is supportive. Public education, rodent control and the use of personal protective measures are key to avoid infections in at-risk populations.

## Introduction

*A 26 year old Canadian woman from the prairies was admitted to the intensive care unit in acute respiratory distress. She was previously healthy with no significant past medical history other than two normal pregnancies and deliveries; she had no allergies, no family history of asthma and no history of trauma. Approximately a week prior to admission she had started to feel unwell with a headache and low grade fever. One day prior to admission she began to have a dry cough and then increasing shortness of breath. On careful questioning, the husband had noted the only unusual event that occurred approximately two weeks before the onset of symptoms was that she had cleaned out their old garage, removing everything and then vacuuming it. At this time she had commented on the abundance of mouse droppings in the garage. An astute clinician sent blood samples to the National Microbiology Laboratory for diagnostic testing for hantavirus. Despite aggressive ventilator support and careful fluid administration, she developed overwhelming pulmonary edema, went into shock and died 24 hours after admission. Her infection with Sin Nombre virus was established by molecular and serological testing thus confirming that she had contracted hantavirus pulmonary syndrome.*

Hantavirus pulmonary syndrome also known as hantavirus cardiopulmonary syndrome (HCPS) is a rare respiratory illness associated with the inhalation of aerosolized rodent excreta (urine and feces) contaminated by hantavirus particles (1,2). Until recently, only four to six cases of hantavirus pulmonary syndrome were diagnosed per year in Canada. Most cases have occurred in Alberta but cases have also been reported in British Columbia, Saskatchewan, Manitoba and Québec (3, 4). In the past two years there has been a substantial increase in the yearly total of hantavirus pulmonary syndrome cases diagnosed in Canada. All cases occurred in rural settings and approximately 70% of the cases have been associated with domestic and farming activities.

The objective of this paper is to review the clinical features and laboratory diagnosis of this disease hantavirus pulmonary syndrome and describe the epidemiologic trends that have been observed in Canada between 1994 and 2014.

Although four hantavirus species have been implicated as etiological agents of hantavirus pulmonary syndrome in North America (5), the Sin Nombre virus is most commonly associated with hantavirus pulmonary syndrome in Canada and the United States and its primary reservoir is the deer mouse, Peromyscus maniculatus (3, 6).

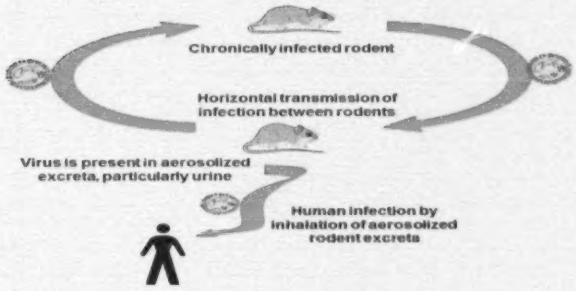
## Sin Nombre virus

The Sin Nombre virus is a member of the Hantavirus genus (Family Bunyaviridae) (7, 8). The Bunyaviridae family is comprised of a large and diverse group of RNA viruses with a tripartite genome composed of S, M and L segments. The family is currently composed of five genera, *Orthobunyavirus*, Nairovirus, Phlebovirus, Tospovirus and Hantavirus, all of which contain viruses of agricultural or medical importance. The hantavirus genus was conceived in 1983 and currently, the International Committee on the Taxonomy of Viruses recognizes more than 20 unique species within the hantavirus genus (7, 8). Approximately half of these species are associated with human diseases such as hemorrhagic fever with renal syndrome and hantavirus pulmonary syndrome. Spill-over is very rare and each hantavirus species is typically associated with a single rodent reservoir; co-evolution with rodent hosts has probably occurred for thousands and perhaps millions of years (8, 9).

### Transmission and incubation

Sin Nombre virus is most frequently associated with inhalation of contaminated excreta. This is primarily from deer mice urine and less often with feces (4, 10, 11, 12) (**Figure 1**). The virus is also found in saliva and therefore bites are a potential route of transmission; however, few cases directly associated with mouse bites have been documented. Person-to-person transmission of hantavirus pulmonary syndrome has not been documented in North America but has been associated with Andes hantavirus infections in Chile and Argentina (9). Interestingly, person-to-person transmission of Andes hantavirus occurs mainly in family clusters and transmission risk is associated with close contact activities including sexual contact during the disease prodrome; nosocomial infections are rare but have been reported (13). The incubation period of hantavirus pulmonary syndrome has been determined to be between 9 and 33 days with a median time of symptom onset of 14 to 17 days post-exposure, although incubation periods between 46 to 51 days have been reported (14, Drebot, unpublished observation).

**Figure 1: Illustration of the typical cycle of transmission of hantaviruses**


Chronically infected rodent
Horizontal transmission of infection between rodents
Virus is present in aerosolized excreta, particularly urine
Human infection by inhalation of aerosolized rodent excreta

### Clinical features

Hantavirus pulmonary syndrome is characterized by four phases of disease: febrile prodrome, cardiopulmonary, diuretic and convalescent (1, 14, 15). Upon inhalation of Sin Nombre virus contaminated excreta, an extensive infection of pulmonary endothelial cells occurs and viremia is initiated (14). Following the incubation period, individuals usually experience the febrile prodrome characterized by fever, chills, occasional headaches and sometimes gastrointestinal symptoms.

Clinical illness is characterized by a febrile illness (>38.3° C) with bilateral diffuse interstitial edema that radiographically resemble acute respiratory distress syndrome. Respiratory compromise requiring supplemental oxygen often develops within 72 hours of hospitalization (1). Thrombocytopenia and elevated hematocrit levels are highly sensitive and specific features in detecting hantavirus pulmonary syndrome in suspect patients (16). Three to six days after the onset of initial symptoms the patient will enter the cardiopulmonary phase, typically manifesting with cough and shortness of breath; pulmonary edema and deterioration of cardiopulmonary function may then rapidly occur over the ensuing 24 hours. Death can occur within 48 hours due to respiratory failure, myocardial dysfunction and shock. Those who get through the cardiopulmonary phase proceed to the third (diuretic) phase and their prognosis is much better. Over two to four days, these patients rapidly improve, their symptoms resolve and so does their pulmonary edema. The final convalescent phase can last for months with persistent weakness, fatigue and abnormal pulmonary function (1, 4).

### Treatments and vaccines

There are no proven antiviral therapies for hantavirus pulmonary syndrome and vaccines are currently not available (17). Clinical management depends on careful fluid administration and ventilatory support. If available, the use of extracorporeal membrane oxygenation for advanced hantavirus pulmonary syndrome is a consideration. Generally extracorporeal membrane oxygenation is reserved for advanced hantavirus pulmonary syndrome and has historically been associated with poor survival rates. The procedure has been used with a significant degree of success at the University of New Mexico with almost 70% of severe cases recovering after treatment but must be initiated quickly once advanced shock or respiratory failure develops (14,17).

### Risk factors and prevention

Risk factors for infection with hantaviruses usually include involvement in outdoor activities such as rural- and forest-related activities, peridomestic infestation of premises by rodents, exposure to potentially infected dust and outdoor military training (18). Case-control studies in the US, have identified peridomestic cleaning, agricultural activities and increased numbers of small mammals within households as risk factors for hantavirus pulmonary syndrome (19,20) as well as entering or cleaning rarely used, rodent-infested structures (21). Key components of prevention are focused on safe rodent handling, disinfection and rodent exclusion methods (22) and disease prevention is primarily delivered through public education. Personal risk reduction measures include recognizing rodents / evidence of rodent infestation, preventing rodents from entering the home, use of appropriate procedures (e.g., ventilation) and the use of personal protective equipment and disinfectants when cleaning or entering areas contaminated with mouse droppings (3,22).

### Laboratory diagnosis

Laboratory criteria for diagnosis includes any of the following: presence of hantavirus-specific IgM or a fourfold or greater increase in IgG antibody titres, a positive reverse transcriptase-polymerase chain reaction (RT-PCR) amplification of viral RNA, or a positive immunohistochemical result for hantavirus antigen in a patient's tissue. Isolation of the virus from clinical samples is difficult and is not usually carried out during investigations of suspect cases (1, 4, 14).

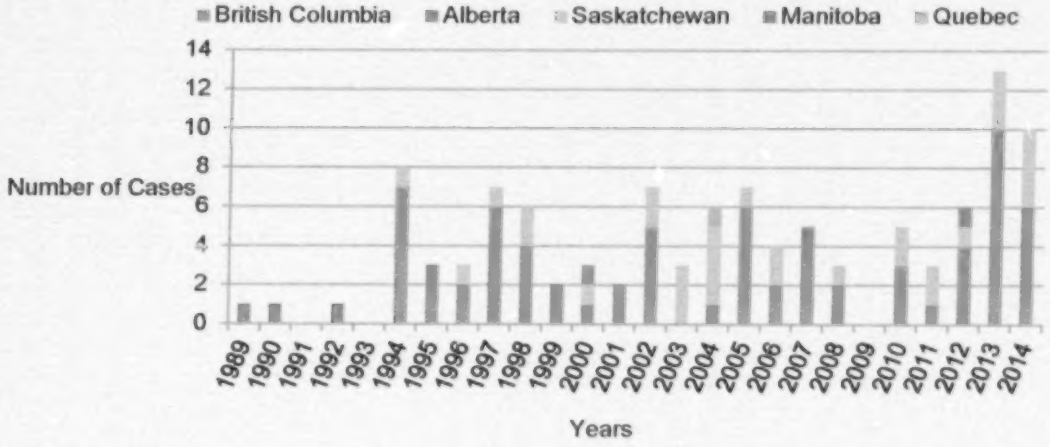
The gold-standard diagnosis of hantavirus pulmonary syndrome is based upon the detection of hantavirus-specific antibodies (4). Antibodies of the immunoglobulin (Ig) M class are present during the earliest clinical stages of hantavirus pulmonary syndrome. IgG antibodies against structural Sin Nombre virus proteins such as the nucleocapsid (N) or G1 /Gn glycoprotein can quite often be detected even in the prodrome phase (1,4).

## Epidemiology in Canada

Canada has adopted the hantavirus pulmonary syndrome case definition recommended by the Pan American Health Organization (1). A confirmed case is a person with clinical illness and laboratory confirmation of infection. Active surveillance for hantavirus pulmonary syndrome began in 1994 and it was made a nationally notifiable disease in January 2000 (3). As of December 31, 2014 a total of 109 laboratory-confirmed cases of hantavirus pulmonary syndrome have been documented in Canada (Kobinger, Grolla, Jones, Lindsay, Drebot and Strong, unpublished observation) and over 600 cases have been identified in the US (6,23). An average of four to five hantavirus pulmonary syndrome cases have been diagnosed annually with yearly numbers fluctuating between 0

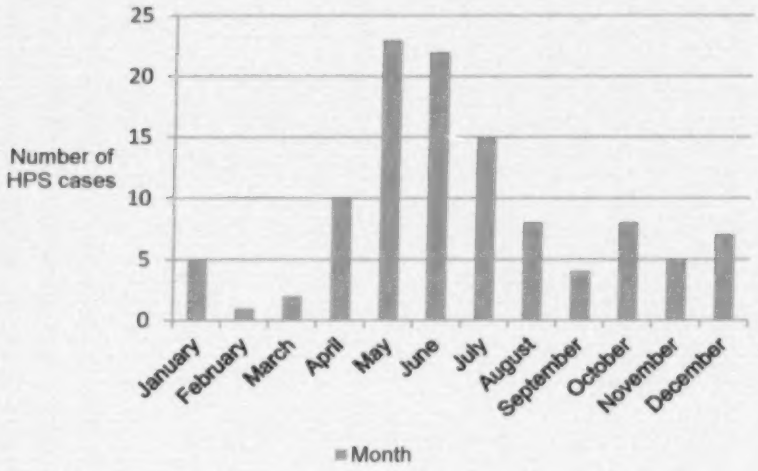
and 13 cases (**Figure 2**). Three retrospective cases were identified in 1989, 1990 and 1992 after active surveillance was initiated in 1994.

**Figure 2: Distribution and total number of hantavirus pulmonary syndrome cases (n=109) reported in Canada, 1989 to 2014**




In 2013 and 2014, there were 13 and 10 cases identified respectively; a marked increase in hantavirus pulmonary syndrome cases compared to previous years (**Figure 2**). Cases of hantavirus pulmonary syndrome have been diagnosed in every month, although there is an obvious spring and early summer peak of infections, with over 60% of the cases occurring between April and July (**Figure 3**). The average age of cases has been 40 years old (range seven to 76) and the majority of cases have been male (67%, 74/109). The current documented case fatality rate in Canada is 29% (30/105) (the outcome of four patients is unknown), with higher mortality rates observed in females (39%) compared with males (24%). Case numbers and mortality rates are typically lower for children (zero to 10 years of age) and elderly individuals (60+ years), with the majority of infections occurring in teenagers (13 to 19 years old; 9.1% of all hantavirus pulmonary syndrome cases), young adults (20 to 40 years old; 33.6%) and middle-aged (41 to 60 years old; 50%) individuals. A similar age-specific pattern of hantavirus pulmonary syndrome cases has been reported in the United States (6) and it is unclear why children appear to be at lower risk for hantavirus pulmonary syndrome. It should be noted that mild and subclinical cases of hantavirus pulmonary syndrome can occur for a minority of infections, so physicians should be aware of a wider spectrum of disease severity (24, 25).

**Figure 3: Seasonal distribution of hantavirus pulmonary syndrome cases (HPS) in Canada (n=109)**




Despite the detection of Sin Nombre virus-infected mice from across Canada, 99% of the cases of hantavirus pulmonary syndrome have occurred in the four western provinces either within or on the edge of the Western Plains geographic area. Only a single case has been reported in eastern Canada (Québec) (**Figure 2**). Alberta accounts for over half the hantavirus pulmonary syndrome cases diagnosed with 60 of the 109 cases reported (55%). A similar western-biased spatial pattern of hantavirus pulmonary syndrome cases is observed in the US (6, 23, 26). Spatial clustering of hantavirus pulmonary syndrome cases does occur and multiple human infections associated with a common exposure to rodent droppings (e.g., a cleaning event) have been observed on two occasions (27). Nucleotide sequence analysis of Sin Nombre virus M and S genomic segments from infected deer mice collected in Canada has demonstrated genetic polymorphisms / fingerprints which correlate with the geographic location of collection (28). However, it is uncertain if western strains of the Sin Nombre virus are more virulent than eastern strains, or if other, as yet undetermined factors, are responsible for the disproportionate number of cases of hantavirus pulmonary syndrome occurring in western Canada. The genetics of deer mouse populations and inherent differences in viral prevalence of Sin Nombre virus are other factors that may play a role in the disjunctive distribution of hantavirus pulmonary syndrome cases in Canada and warrant further investigation (28).

Two imported cases of hantavirus pulmonary syndrome (one each from Bolivia and Argentina) have also been reported in Canada (4, 29). One of the imported cases involved a Canadian who had travelled to Argentina and became ill a week after arriving back at his residence in Saskatchewan. The individual was diagnosed by serological testing as having been exposed to a hantavirus and died shortly after being identified as an hantavirus pulmonary syndrome case. The patient had spent several weeks in Argentina, however it was possible that the individual had been infected upon his return to Canada. Determining the country where he was actually exposed could not be initially verified due to the possible serological cross reactivity of Canadian and South American hantaviruses. The identification and phylogenetic characterization of hantavirus RNA in the patient's blood clots verified that the infection was associated with an Argentinean hantavirus related to the Andes virus lineage. The use of PCR and amplicon sequencing not only verified the country in which the patient was exposed to the virus but also provided a timeline that indicated an incubation period of over a month between exposure and symptom onset. Similar molecular epidemiology procedures were used to identify the imported case from Bolivia (29).

## Molecular epidemiology

Although genetic identification and characterization of the infecting virus is not always possible, when appropriate samples (e.g., acute whole blood) are available and polymerase chain reaction amplicon sequencing is performed, Sin Nombre virus has always been identified as the etiological agent of hantavirus pulmonary syndrome in Canada. Consistent with previous phylogenetic characterization of Sin Nombre virus from infected

deer mice in Canada, the genotype of the virus associated with hantavirus pulmonary syndrome cases corresponds with a western Canadian genogroup / clade ((28), Grolla et al, unpublished observation). Field investigations involving the comparisons of virus sequences from mice collected near where patients have resided / worked have demonstrated a high degree of genetic relatedness and in certain instances exact matches (Drebot and Lindsay, unpublished observation). The ability to identify mice carrying the strain of virus associated with a hantavirus pulmonary syndrome case may assist in distinguishing among multiple sites of possible exposures (including verification of imported cases). The elegant epidemiological investigation conducted by Jay et al. 1995 (30) demonstrates the utility that molecular epidemiology has to improve our understanding of the risk factors (and point sources for infection) associated with hantavirus infection (31).

### Rodent surveillance

In Canada, the ubiquitous deer mouse is the primary reservoir for Sin Nombre virus while other species of hantaviruses have been detected (e.g., Prospect Hill virus) in red-backed voles (3). To date, disease has not been associated with non-Sin Nombre virus species in Canada (Strong, Golla, Kobinger and Drebot, unpublished observation). Based on passive surveillance for hantaviruses in rodents, Sin Nombre virus-infected mice have been detected in every province except Prince Edward Island and Nova Scotia (3, 28). To-date, there is evidence of Sin Nombre virus-infected mice in Yukon but not in the Northwest Territories or Nunavut. However, only limited numbers of deer mice have been tested from the Northwest Territories, therefore Sin Nombre virus may be circulating in this and other regions of Canada. The distribution of Sin Nombre virus-infected mice is discontinuous and focal with some deer mouse populations uninfected while others, in relatively close proximity, displaying high rates of seroprevalence (>30% [3]).

## Discussion

Hantavirus pulmonary syndrome is a rare disease; however, there has been a surge in cases noted in the last two years indicating that there continues to be a risk for infection in Canadian localities where the virus circulates. The majority of exposures to Sin Nombre virus result in severe disease, but hantavirus infections should also be considered in the differential diagnosis for nonspecific febrile illness. This is especially relevant for persons with known exposure to rodents or their excreta, usually as a result of cleaning, rodent-infested structures in western Canada (3). In addition, it is possible that cases without severe pulmonary involvement may have gone undiagnosed for a minority of patients (24, 25, 27).

Sin Nombre virus infects deer mice across Canada; however, almost all human cases of hantavirus pulmonary syndrome occur in the western provinces of British Columbia, Alberta, Saskatchewan and Manitoba. Although case numbers are low relative to other infectious diseases, the fatality rate remains at approximately 30% despite increased awareness of hantavirus pulmonary syndrome. Cases of hantavirus pulmonary syndrome have been reported in every month of the year but most occur in the spring and early summer. Seasonal specific-risk factors related to cleaning of structures (e.g., cottage- or farm-associated machinery or buildings) and the increased potential contact with deer mouse excreta at this time of year likely contributes to the seasonality of hantavirus pulmonary syndrome cases (3,6,32).

The number of hantavirus pulmonary syndrome cases in Canada has noticeably increased over the last two years and this trend should be closely monitored. The reason for the higher numbers of hantavirus pulmonary syndrome cases remains unclear; however, it is speculated that the recent upswing in hantavirus pulmonary syndrome cases could be driven by atypically large deer mouse populations that may have resulted from milder winters and an associated increase in reproductive output of local deer mouse populations. Larger infected mouse populations may have led to increased opportunities for human exposure to infected excreta and hence a higher risk of transmission of hantavirus infection to humans (12).

## Conclusion

Hantavirus pulmonary syndrome is a rare rodent-borne disease that occurs primarily in western North America, Central America and South America. Prevention of this disease can be achieved through public education about the risks associated with exposure to rodents and their excreta and the use of appropriate preventive practices. Public health authorities should continue to update and modify existing messaging in order to enhance the uptake

of key protective behaviours by at-risk populations in Canada. Travellers should also be reminded of the risk of hantaviruses and actions to prevent infection while abroad as imported cases of hantavirus pulmonary syndrome have been reported (4, 29). Several key research questions remain unanswered including why the number of HPS cases have increased in recent years as well as why the majority of cases occur in the western provinces (and states) despite the fact that Sin Nombre virus-infected deer mice have been identified across Canada.

## Acknowledgements

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## Conflict of interest

None.

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# Surveillance for Lyme disease in Canada, 2009 to 2012

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## Abstract

**Objectives:** To summarize the first four years of national surveillance for Lyme disease in Canada from 2009 to 2012 and to conduct a preliminary comparison of presenting clinical manifestations in Canada and the United States

**Methods:** The numbers and incidence of reported cases by province, month, year, age and sex were calculated. Logistic regression was used to examine trends over time. Acquisition locations were mapped and presenting clinical manifestations reported for jurisdictions where data was available. Variations by province, year, age and sex as well as presenting clinical symptoms were explored by logistic regression. An initial comparative analysis was made of presenting symptoms in Canada and the United States.

**Results:** The numbers of reported cases rose significantly from 144 in 2009 to 338 in 2012 (coefficient = 0.34, standard error = 0.07, P <0.05), mostly due to an increased incidence of infections acquired in Canada. More cases were classified as 'confirmed' (71.5%) than 'probable' (28.5%). Most cases occurred in locations where vector tick populations were known to be present. More men than women were affected (53.4% versus 46.6%), incidence was highest in adults aged 55 to 74 years and in children aged five to 14 years. Most cases (95%) were acquired from April to November. Of cases acquired in endemic areas, 39.7% presented with manifestations of early Lyme disease, while 60.3% had manifestations of disseminated Lyme disease. There were significant differences among age groups, sexes and provinces in the frequencies of reported clinical manifestations. The proportion of cases acquired in endemic areas presenting with early Lyme disease was lower than that reported in the US.

**Conclusion:** Lyme disease incidence is increasing in Canada. Most cases are acquired where vector tick populations are spreading and this varies geographically within and among provinces. There is also variation in the frequency of age, season and presenting manifestations. The lower proportion of cases presenting with early Lyme disease in Canada compared with the US suggests lower awareness of early Lyme disease in Canada, but this requires further study.

## Introduction

Lyme disease, caused by the bacterium *Borrelia burgdorferi sensu stricto* in North America is transmitted to humans from wild animal reservoir hosts by Ixodes spp. ticks (1) in their woodland habitats (2). Lyme disease risk in Canada occurs where tick vectors are established in southern British Columbia (where the relatively inefficient tick vector Ixodes pacificus occurs) and in southern parts of central and eastern Canada into which the efficient tick vector I. scapularis is spreading from the United States, driving Lyme disease emergence in Canada (3). Low-

level Lyme disease risk occurs over a wider geographic area due to ticks dispersed from tick populations by migratory birds (4, 5).

In light of the documented northern migration of ticks into Canada, Lyme disease became nationally notifiable in Canada in 2009 and basic information on human cases is submitted by all provinces and territories to the National Notifiable Disease Surveillance System (NNDSS) coordinated by the Public Health Agency of Canada (PHAC). A Lyme Disease Enhanced Surveillance (LDES) system was initiated by PHAC in 2010 with provincial public health organizations to obtain more detailed data on Lyme disease cases. Together, these surveillance systems aim to identify changing trends in Lyme disease incidence, the Canadian population at risk and the types of clinical disease in Canada to inform clinician-based Lyme disease diagnosis and reporting.

In this study, data from the first four years of national surveillance for Lyme disease (2009 to 2012) are presented and analyzed to describe the early patterns of Lyme disease emergence in Canada. As Lyme disease emergence in central and eastern Canada is likely an extension of the emergence of Lyme disease in the US, patterns of Lyme disease cases (age, season of acquisition and presenting manifestations) were compared against those reported in the United States.

## Methods

### Human case data sources

NNDS data on annual numbers of cases reported to all provincial and territorial public health organizations by clinicians or via provincial laboratories were available for 2009 to 2012. Basic information reported included sex, age and episode date. The cases were classified as 'confirmed' or 'probable' by the provincial public health organizations submitting the data, except for British Columbia, Québec and New Brunswick who reported all cases without classifying them and did not report cases with erythema migrans rashes without laboratory support for the diagnosis.

**The national surveillance case definition of Lyme disease (6)**

**Confirmed case**

Clinical evidence of illness with laboratory confirmation by:

• Isolation of *Borrelia burgdorferi* from an appropriate clinical specimen, OR

• Detection of *B. burgdorferi* DNA by polymerase chain reaction, OR

• A positive serologic test result using the two-tier (ELISA and Western Blot) test with a history of residence in or visit to a Lyme disease-endemic area.*

**Probable case**

**P1** = Clinical evidence of illness with a positive serologic test result using the two-tier (ELISA and Western Blot) test, without a history of residence in, or visit to, a Lyme disease endemic area*

OR

**P2** = Clinician-observed erythema migrans without laboratory evidence but with history of residence in, or visit to, a Lyme disease endemic area.[1]

[1]Lyme disease endemic areas are locations where tick populations have become established (as confirmed by multiple site visits) and are transmitting *B. burgdorferi* among wild animal hosts (7). Increasingly, due to the cost of multiple site visits, environmental risk of Lyme disease is defined as 'risk areas' where tick presence has been detected by field surveillance but not confirmed by multiple site visits (3).

In 2010, the LDES was implemented in partnership with the provinces of Manitoba, Ontario, New Brunswick and Nova Scotia. In 2012, Alberta, Saskatchewan and Prince Edward Island joined. Data transferred in a standard form in the LDES included details of possible location of acquisition of infection within or outside Canada, details of clinical manifestations and methods of laboratory diagnosis. There were variations among provinces participating in the LDES in the data provided (**Appendix 1**).

## Clinical manifestations

Information on clinical features was provided by Manitoba, Ontario, New Brunswick and Nova Scotia, although Manitoba reported only two categories of symptoms: erythema migrans and 'other clinical evidence'; i.e., evidence of disseminated Lyme disease but without further details on symptoms. Categories of clinical manifestations were those of early Lyme disease (i.e., erythema migrans), early disseminated Lyme disease including manifestations of neuroborreliosis (Bell's palsy or other neurological manifestations of disseminated Lyme disease), cardiac manifestations and manifestations of late disseminated Lyme disease such as arthritis. (See **text box** below.) Note that it was assumed that all "P2" probable cases (i.e., cases with erythema migrans but no serological test result) were early Lyme disease having a single erythema migrans rather than multiple erythema migrans lesions (which occur in disseminated Lyme disease). Cases with multiple erythema migranswould be expected to have positive serological test results and be captured as confirmed or "P1" probable cases.

### Main manifestations of Lyme disease (8)

**Early localized**: Erythema migrans +/- fever, arthralgias and headache

**Early disseminated**: Multiple erythema migrans +/- fever, arthralgias, headache and lymphadenopathy

**Cardiac:** AV block, tachyarrhythmias, myopericarditis, myocardial dysfunction

**Neurologic**: Aseptic meningitis, cranial neuropathy (e.g., Bell's palsy), motor or sensory radiculopathy

**Late disseminated**: Oligoarticular arthritis

**Neurologic:** Encephalopathy, axonal polyradiculoneuropathy, chronic encephalomyelitis[1]

[1]Neurological manifestations of late Lyme disease are very uncommon (9), so for parsimony in collection and transfer of data, all cases of Lyme disease with neurological manifestations were considered as early disseminated Lyme disease.

## Data analyses

The data from both the LDES and NNDSS were summarized and, where possible, compared against similar data on Lyme disease case surveillance from the US (10) where similar data have been collected for over 20 years. Annual incidence in Canada, as well as province-, sex- and age group-specific incidence rates was calculated per 100,000 population. The denominators were census population estimates for July 1st for each year from 2009 to 2012 (11). The proportion of cases reported by month and by case classification for each year was also calculated. Trends in the numbers of cases reported nationally for the period 2009 to 2012 ('confirmed' and 'probable' cases combined) were explored by logistic regression using weighted least squares estimation in Stata SE 11.0 for Windows (College Station, Tx), with year as the explanatory variable accounting for recent Canadian population estimates (12). Analysis was conducted with case numbers and data reported at the time but these may change slightly due to retrospective identification of cases.

Analysis of numbers of endemic versus travel-related cases, location of acquisition and clinical features were performed on cases reported via the LDES by Manitoba, Ontario, New Brunswick and Nova Scotia.
The likely locations of exposure of cases in Canada were mapped using ArcGIS Version 10.2 (ESRI) with point locations being the centroid of Forward Sortation Areas (**Table 1**) or endemic areas depending on reported location of acquisition. Known endemic areas and risk areas (3) were also mapped for visual comparison.

**Table 1: Lyme disease cases by classification and year, 2009 to 2012**

| Case classification | Year | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 2009 | | 2010 | | 2011 | | 2012 | | Total | |
| | N | (%) | N | (%) | N | (%) | N | (%) | N | (%) |
| **All cases** | | | | | | | | | | |
| **Confirmed** | 115 | (79.9) | 107 | (74.8) | 188 | (70.7) | 227 | (67.2) | 637 | (71.5) |
| **Probable** | 29 | (20.1) | 36 | (25.2) | 78 | (29.3) | 111 | (32.8) | 254 | (28.5) |
| **Total** | 144 | 100 | 143 | 100 | 266 | 100 | 338 | 100 | 891 | 100 |
| **Cases acquired in Canada with clinical data[1]** | | | | | | | | | | |
| **Confirmed** | 44 | (81.5) | 43 | (68.3) | 79 | (61.7) | 93 | (65.5) | 259 | (66.9) |
| **All probable cases** | 10 | (18.5) | 20 | (31.7) | 49 | (38.3) | 49 | (34.5) | 128 | (33.1) |
| First probable case definition | 8 | (14.8) | 15 | (23.8) | 40 | (31.3) | 24 | (16.9) | 87 | (22.5) |
| Second probable case definition | 2 | (3.7) | 5 | (7.9) | 9 | (7.0) | 25 | (17.6) | 41 | (10.6) |
| **Total** | 54 | 100 | 63 | 100 | 128 | 100 | 142 | 100 | 387 | 100 |

[1]Cases for which detailed clinical data (symptoms and laboratory diagnosis information) and exposure information was available to distinguish the two different probable case definitions.

Variations among provinces, years, age groups and sex in the proportions reporting different clinical manifestations of disseminated Lyme disease were explored in logistic regression models in Stata SE 11.0. The outcome variables were presence/absence of erythema migrans, neurological manifestations, cardiac manifestations and arthritis/joint swelling in separate models. Explanatory variables of age, year, province and sex were first explored in bivariable analyses and those showing associations with the outcome at a level of significance of $P < 0.1$ were included in multivariable models. Polynomial relationships of age with frequency of manifestations (using age and age squared as explanatory variables) were explored as suggested by visual inspection of Lowess smoothed graphs of these relationships. The most parsimonious multivariable models were sought by backward elimination of variables. The level of significance for the multivariable model was $P < 0.05$.

## Results

### Incidence and temporal trends

The numbers of reported cases rose significantly from 144 in 2009 to 338 in 2012 (coefficient = 0.34, standard error = 0.07, $P < 0.05$; **Table 1**), with incidence rising from 0.4 to 1.0 per 100,000 population (**Table 2**).

**Table 2: Incidence of reported Lyme disease cases by province and year, 2009 to 2012**

| Province | Year | | | |
|---|---|---|---|---|
| | 2009 | 2010 | 2011 | 2012 |
| **All cases** | | | | |
| British Columbia | 0.2 | 0.2 | 0.4 | 0.4 |
| Alberta | 0.0 | 0.0 | 0.2 | 0.2 |
| Saskatchewan | 0.0 | 0.0 | 0.1 | 0.0 |
| Manitoba | 0.4 | 1.0 | 1.0 | 1.5 |
| Ontario | 0.8 | 0.7 | 1.0 | 1.4 |
| Québec | 0.2 | 0.1 | 0.4 | 0.5 |
| Prince Edward Island | 0.0 | 0.0 | 0.7 | 1.4 |
| New Brunswick | 0.0 | 0.3 | 0.7 | 0.9 |
| Nova Scotia | 1.7 | 1.8 | 5.7 | 5.4 |
| Newfoundland and Labrador | 0.0 | 0.2 | 0.0 | 0.0 |
| **Canada** | 0.4 | 0.4 | 0.8 | 1.0 |
| **Cases acquired in Canada**[1] | | | | |
| Saskatchewan | 0.0 | 0.0 | 0.1 | 0.0 |
| Manitoba | 0.3 | 0.6 | 0.6 | 1.0 |
| Ontario | 0.5 | 0.5 | 0.8 | 0.8 |
| Prince Edward Island | 0.0 | 0.0 | 0.0 | 0.7 |
| New Brunswick | 0.0 | 0.3 | 0.4 | 0.7 |
| Nova Scotia | 1.5 | 1.5 | 5.2 | 5.3 |

[1]British Columbia and Québec did not provide information on whether cases were acquired in Canada or during travel outside Canada. All cases in Alberta and Newfoundland and Labrador were all acquired during travel outside Canada.

Cases were reported from all provinces with most infections acquired in Canada occurring in British Columbia, Manitoba, Ontario, Québec, New Brunswick and Nova Scotia. All cases reported from Alberta and Newfoundland and Labrador were reported as acquired during travel outside Canada.

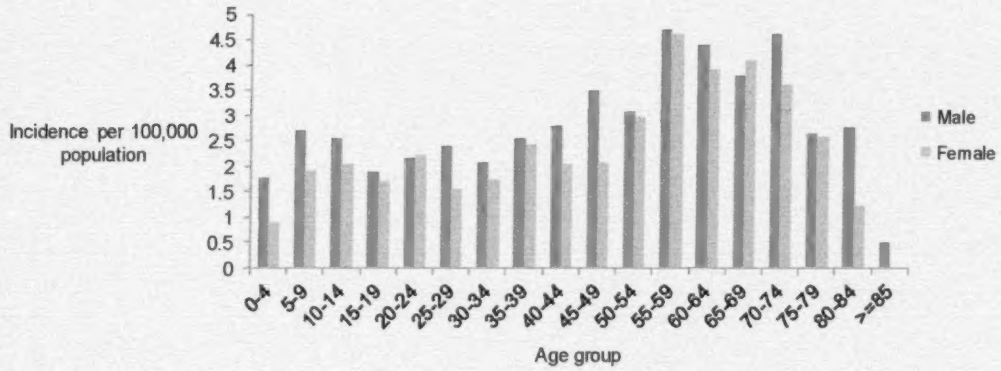
In 2012, incidence was >1.0 per 100,000 population in five provinces; Manitoba, Ontario, New Brunswick, Nova Scotia and Prince Edward Island (**Table 2**). Incidence increased primarily in Manitoba, Ontario, Québec, New Brunswick and Nova Scotia (**Table 2**). There was a slight decrease of the number of cases reported in British Columbia and Nova Scotia from 2011 to 2012.

The majority of cases were reported as 'confirmed' (**Table 1**). Of the cases without a reported history of travel outside Canada, 387 included data on clinical symptoms and likely location of infection. For these cases, (reported by Manitoba, Ontario, New Brunswick and Nova Scotia), the numbers of P1 and P2 'probable' cases could be estimated. For these provinces, most probable cases were of the P1 category (**Table 1**).

## Incidence variation with age and sex

Incidence varied among age groups, being highest in older adults from 55 to 74 years and in children (those cases with reported ages less than 18) being highest in the five to 14 year age range (**Figure 1**). More cases were reported as males (476/891, 53.4%) than females (409/891, 46.6%), which was consistent for most (16/18) age groups (**Figure 1**).

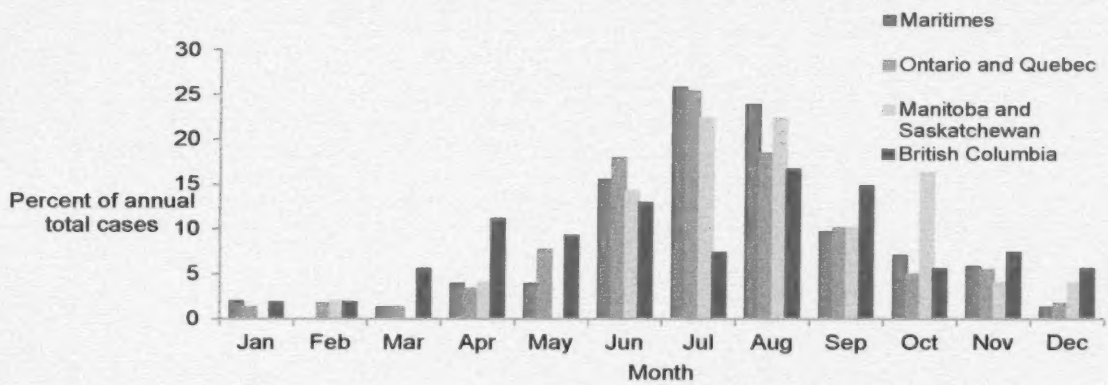
**Figure 1: The incidence of reported Lyme disease cases per 100,000 population during 2009 to 2012 by age and sex**




## Seasonality

Of 387 cases for which the type of episode date was recorded, the episode date was date of onset of illness for 328 (84.7%), date of specimen collection for diagnosis for 42 (10.8%), date of clinical or laboratory diagnosis for 13 (3.3%) and date of reporting for 3 (0.8%). Lyme disease cases had episode dates in all months of the year, but most (544/891, 61.1%) occurred from June to August (**Figure 2**). Cases in British Columbia tended to occur earlier and later in the year than in other provinces, while a greater proportion of cases occurred in October in Manitoba compared to other provinces (**Figure 2**).

**Figure 2: The proportions of Lyme disease cases reported from 2009 to 2012 and acquired in Canada by episode date[1]**

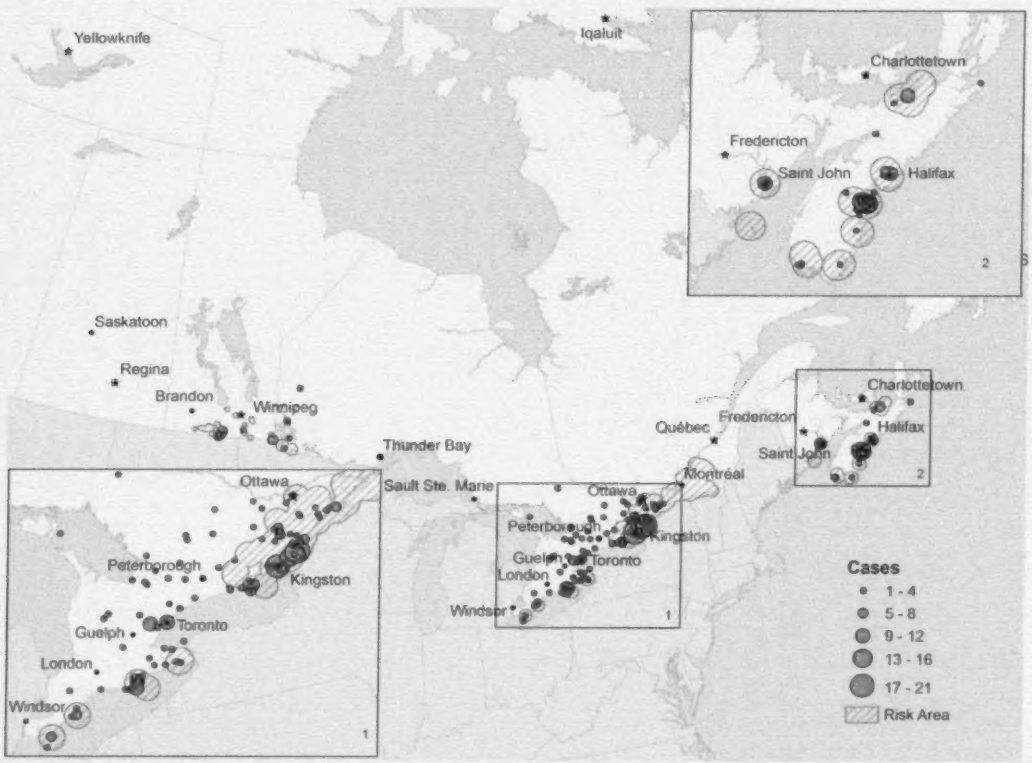



[1] Where date of onset of illness was not available, date of diagnosis or specimen collection for laboratory diagnosis were used as the

## Geographic location of acquisition

Most cases acquired in Canada were acquired in areas where known endemic areas or risk areas occur, although cases were reported to occur outside these locations (**Figure 3**). The annual numbers of cases reported as acquired outside Canada from 2009 to 2012 was stable: between 38 to 48 cases per year from 2009 to 2012. For the 54 cases reported from 2009 to 2012 for which the location of travel out of Canada was provided, 38 (70.4%) were acquired in the US and 16 (29.6%) were acquired in Europe.

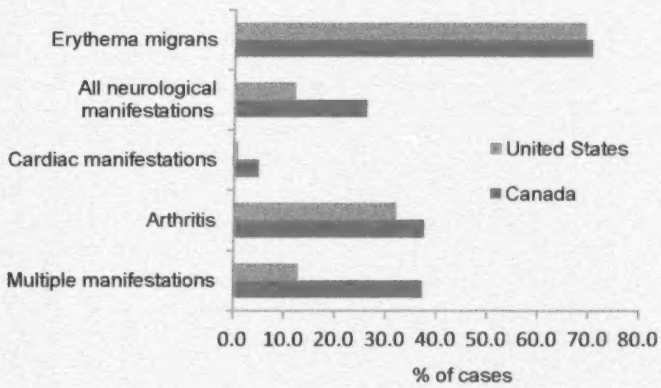
**Figure 3: The reported location of acquisition of Lyme diseases acquired in Canada from 2009 to 2012**




## Clinical manifestations

Of the 353 cases for which information on all five categories of clinical manifestations were available, 157 (44.4%) reported erythema migrans alone (and were therefore early Lyme disease) and a further 92 reported EM with manifestations of disseminated Lyme disease. Manifestations of early disseminated Lyme disease were reported for 98 cases (27.8%) for which the following symptoms were reported: 92 cases (26.1%) reported neurological manifestations (Bell's palsy was reported for 30 cases [8.5%] and other neurological manifestations for 74 cases [21.0%]) and cardiac manifestations for 17 cases (4.8%) (**Figure 4**). Manifestations of late disseminated Lyme disease, e.g., arthritis, were reported for 133 cases (37.8%) (**Figure 4**). Multiple manifestations were reported for 131 cases (37.2%). Of all the reported cases with disseminated Lyme disease, the proportion of cases reporting neurological, cardiac and arthritis manifestations were respectively 38%, 7% and 55%.

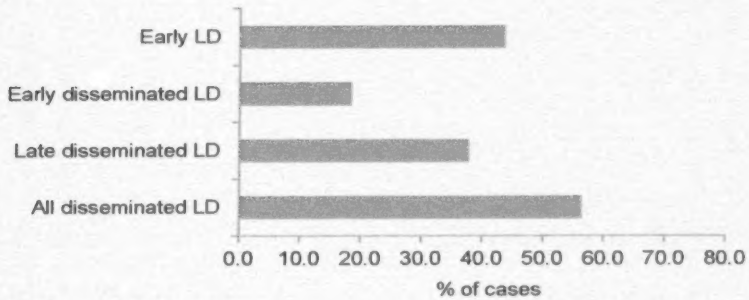
**Figure 4: Percentage of cases reported in the Lyme Disease Enhanced Surveillance with different clinical manifestations of Lyme disease compared against those reported in surveillance in the US (10)[1]**




[1] Note that the total values for each manifestation are shown and that each case may have reported multiple manifestations. The overall proportion reporting multiple manifestations is shown by the lower pair of bars.

According to the surveillance case definitions, cases of early Lyme disease (the "P2" case definition: erythema migrans without laboratory test support for the diagnosis) can only be reported from patients having contact with known Lyme disease-endemic areas. Therefore, to determine the proportions of cases being diagnosed with early Lyme disease versus disseminated Lyme disease (early and/or late), the denominator must be the number of cases with information on clinical manifestations that were reported as having been acquired in known endemic areas. There were 302 cases, with information on clinical manifestations reported as acquired in endemic areas in Manitoba, Ontario, New Brunswick and Nova Scotia. Of these 220 (72.8%) reported erythema migrans, but erythema migrans was the sole manifestation for 120 cases (39.7%), so only 39.7% of cases were reported in early Lyme disease, while the rest (60.3%) had symptoms of disseminated Lyme disease (**Figure 5**). In New Brunswick, cases of erythema migrans without serological support for the diagnosis are not reported, but for four of the nine cases (44.4%) with data on clinical manifestations, erythema migrans was the only clinical manifestation. Therefore possible under-reporting of "P2" probable cases (erythema migrans acquired in an endemic area) in all the provinces was not simply attributable to lack of reporting in New Brunswick. The number of cases during the period 2009 to 2012 from the three provinces reporting information on all five clinical features (Ontario, New Brunswick & Nova Scotia) was 275.

**Figure 5: The percentage of infections acquired in endemic areas reported at different stages of disease according to the clinical manifestations reported in the Lyme Disease Enhanced Surveillance**



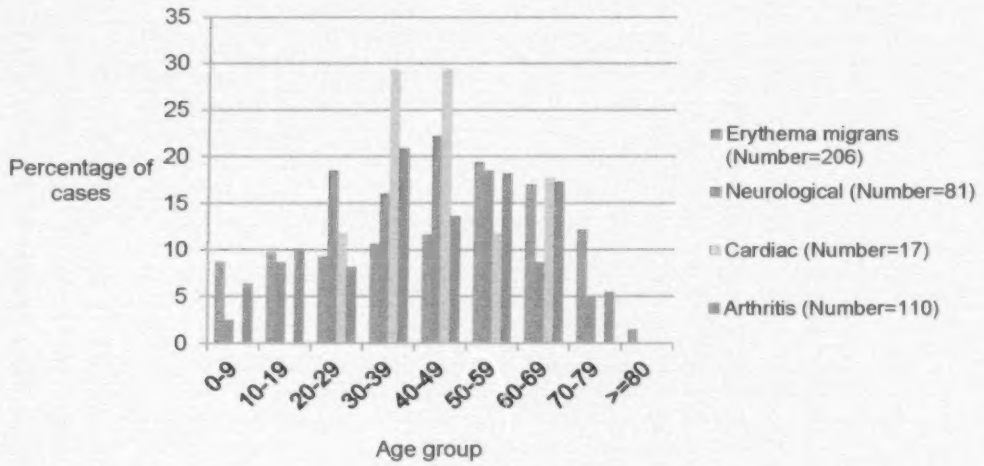

Of the cases acquired in endemic areas, 199 (72%) reported erythema migrans (of which 120 [43.6%] had erythema migrans as the only clinical manifestation), 25 (9.1%) had Bell's palsy, 60 (21.8%) had other neurological symptoms (a total of 74 [26.9%] had neurological symptoms of any kind), 14 (5.1%) had cardiac symptoms and 104 (37.8%) had arthritis or joint swelling. More than one clinical manifestation was reported for 107 (38.9%) cases.
Overall, of cases acquired in endemic areas 120 (43.6%) were early Lyme disease (reported to have erythema migrans as the only manifestation) and 155 (56.4%) were disseminated Lyme disease. Of the disseminated Lyme disease cases 51 (18.5%) were early disseminated Lyme disease (reported to have neurological or cardiac manifestations but not arthritis) and 104 (37.8%) were late disseminated Lyme disease (reported to have arthritis).

The frequency of reported erythema migrans was highest for children and adults >50 years compared to other age groups, although after adjusting for year, the frequency of reporting of erythema migrans increased linearly with age (**Table 3**, **Figure 6**). The frequency of neurological manifestations and cardiac symptom reports varied significantly among age groups. Neurological manifestations were most frequently reported for 20 to 59 year-olds and relatively rarely reported for younger children and adults over 60, while cardiac symptoms were only seen in cases aged 20 to 69, particularly in cases aged 30 to 49 (**Figure 6**). The proportion of cases reporting neurological symptoms was also significantly higher in Ontario than in Nova Scotia and New Brunswick combined and was lower in women than men (**Table 3**). There were no significant differences among ages, sexes, provinces and years in the proportion of cases that reported arthritis (data not shown).

**Table 3: Final multivariable models, following backward elimination of non-significant (P >0.05) variables, for which the outcome variables were the proportion of cases showing erythema migrans, neurological manifestations and cardiac manifestations**

| Variable | Odds ratio | 95% Confidence interval | Wald z | P value |
|---|---|---|---|---|
| Outcome = erythema migrans | | | | |
| Year 2010 versus 2009 | 1.364 | 0.616-3.018 | 0.77 | >0.1 |
| Year 2011 versus 2009 | 2.232 | 1.109-4.489 | 2.25 | <0.05 |
| Year 2012 versus 2009 | 2.860 | 1.416-5.778 | 2.93 | <0.01 |
| Age | 1.015 | 1.004-1.027 | 2.71 | <0.01 |
| Outcome = neurological manifestations | | | | |
| Women versus men | 0.561 | 0.345-0.940 | -2.19 | <0.05 |
| Age | 1.073 | 1.014-1.146 | 2.45 | <0.05 |
| Age squared | 0.998 | 0.998-0.999 | -0.30 | <0.01 |
| Ontario versus New Brunswick and Nova Scotia | 3.781 | 1.849-7.772 | 3.62 | <0.001 |
| Outcome = cardiac manifestations | | | | |
| Age | 1.305 | 1.043-1.632 | 2.33 | <0.05 |
| Age squared | 0.997 | 0.994-0.999 | -2.41 | <0.05 |

**Figure 6: Percentage of cases by age group that showed erythema migrans, neurological manifestations, cardiac manifestations or arthritis/joint swelling[1]**




[1]N indicates the number of cases reported as having clinical manifestations.

## Discussion

The annual number of Lyme disease cases reported in Canada more than doubled from 2009 to 2012. Most of this increase was associated with Lyme disease that was acquired in provinces from Manitoba eastward. This trend and the pattern of change in incidence among provinces is consistent with the geographic spread of I. scapularis and Lyme disease risk in eastern and central Canada, although increasing awareness among the public and health practitioners may be resulting in a greater proportion of reported cases. The reported number of

Lyme disease cases is likely an underestimate due to expected under-reporting of Lyme disease in emerging areas (13) and because early Lyme disease cases can be reported only if acquired in Lyme disease-endemic areas unless supported by laboratory evidence. Cases acquired outside these areas are not reported to public health.

Two thirds of Lyme disease cases were 'confirmed' which is consistent with the risk of acquiring Lyme disease being particularly high in Lyme disease-endemic areas. Tick surveillance (3, 14, 15) shows that the I. scapularis population is expanding its geographic range in Canada and nearly a quarter of reported disseminated Lyme disease cases were acquired in areas not known as endemic areas (and were P1 probable cases). However, most of these cases occurred in 'risk' areas where populations of I. scapularis are emerging (**Figure 3**). In risk and endemic areas, incidence may be much higher (over 25/100,000) than province-level incidence values (16). A small number of Lyme disease cases occurred where I. scapularis populations are not yet known but where little field surveillance has occurred to date to verify their presence or absence.
The incidence of reported cases among adults was highest in those over 54 years of age, in men and in children under 15 years old. This pattern is consistent with US surveillance (10). These age groups and men may be particularly at risk of acquiring Lyme disease. However, children and older adults reported early Lyme disease manifestations more frequently and manifestations of disseminated Lyme disease less frequently, so high incidence in these groups may reflect greater awareness and earlier presentation for diagnosis compared to younger adults.

The seasonality of cases in Canada was similar to that observed in the US (10) and was consistent with tick-borne transmission. I. scapularis and I. pacificus are active from April to November and human outdoor recreational activities in woodlands are also most likely to occur at this time. Nymphal ticks transmit most cases of Lyme disease (17), but cases were acquired in early spring and autumn when adult ticks are most active. Consistent with longer season activity of I. pacificus compared to I. scapularis (18), more cases occurred earlier and later in the year in British Columbia where I. pacificus is the vector. Delays between infection and onset or diagnosis of disseminated Lyme disease could explain reporting of some cases in winter (9), although some early Lyme disease cases had a reported date of onset in winter. Why more Lyme disease cases were reported in autumn in Manitoba compared to other provinces in unclear, as ticks would also be active in other provinces at this time.

Data on the types of Lyme disease cases reported from endemic areas suggests there is suboptimal awareness of Lyme disease among the public and front line medical practitioners. A history of erythema migrans was reported for >80% of cases acquired in known endemic areas. However only 40% of cases were reported during early Lyme disease and 60% were likely disseminated Lyme disease, even though erythema migrans was recorded as a manifestation in many disseminated Lyme disease cases. This suggests that many reported cases of disseminated Lyme disease could have been diagnosed and treated earlier, but either the affected patients did not know what the erythema migrans rash was (and didn't present themselves for diagnosis at this stage) or medical practitioners did not diagnose and treat the cases at this stage. In the US, where awareness among the public and medical practitioners is expected to be greater, >56% of reported cases were early Lyme disease (10).

Overall proportions of clinical manifestations of disseminated Lyme disease cases in Canada were similar to those in the United States. When the proportions of disseminated Lyme disease cases showing neurological manifestations, cardiac manifestations and arthritis (i.e., late Lyme disease) were compared against similar data from the US (10), there were some differences. The proportions that were late disseminated Lyme disease were similar (55% and 50% for Canada and the US respectively), but the proportion of cases reporting neurological symptoms was lower in Canada (38% versus 47% in the US) and the proportion reporting cardiac manifestations was higher in Canada (7% versus 3% in the US). Additional Canadian surveillance data is required to determine whether this is a consistent difference and if it changes over time. Tracking occurrence of Lyme carditis is also important because it has been associated with sudden deaths (19).

Neurological and cardiac manifestations were more likely to be reported for younger adults whereas there was no evidence of age-associated variations in the frequency of reporting arthritis. Neurological manifestations were less likely to be reported for males than females. The reasons for these observations are not clear and require further exploration. Reporting of neurological symptoms was more common in Ontario than the Maritimes possibly due to

different methods of reporting symptoms among provinces or due to geographic variation in *B. burgdorferi* strains (20).

The observations and results of this study represent a first view of Lyme disease surveillance data in Canada and it is too early to make firm conclusions regarding these preliminary trends. It is possible that data on location of acquisition and manifestation of infection in Canada is affected by issues of recall and other inaccuracies. The findings here require further study to be corroborated and to assess causality.

## Conclusion

These data suggest that Lyme disease is emerging in Canada, with most cases occurring in seasons when and locations where Lyme disease risk in the environment is known to occur. Incidence was higher in men, in adults over 54 years old and children under 15 years old. The proportion of cases reported in early Lyme disease was lower than expected suggesting suboptimal awareness of Lyme disease during the surveillance period. Variations among provinces and age groups in the proportions of cases reporting erythema migrans and neurological and cardiac manifestations of disseminated Lyme disease were found, although are at present unexplained.

## Acknowledgements

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## Conflict of interest

None

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## Appendix 1: Data collected in national surveillance for Lyme disease in Canada during the period 2009 to 2012

| Data description | Data type | Provinces supplying data |
|---|---|---|
| Age | Continuous | All |
| Sex | Male/Female | All |
| Case classification | Confirmed/Probable | AB, SK, MB, ON, PEI, NS, NL |
| Episode date | Day, Month, Year | All |
| Type of episode date[1] | Category: Onset/Sample collection/Diagnosis/Report | MB, ON, NB, NS, PEI[5] |
| Travel outside Canada | Yes/No | AB, SK, MB, ON, NB, PEI, NS, NL |
| Exposure to known endemic area in Canada within last 30 days[1] | Yes/No | MB, ON, NB, NS |
| Name/identifier of endemic area in Canada[1] | Geolocator | |
| Exposure to known endemic area outside Canada within last 30 days [1] | Yes/No | MB, ON, NB, NS |
| Name/identifier of endemic area outside Canada[1] | Geolocator | MB, ON, NB, NS |
| Forward sortation area of residence (FSA: the first three digits of postal code)[1,2] | Geolocator | MB, ON, NB, NS |
| Symptoms of early Lyme disease (erythema migrans)[1] | Yes/No | MB, ON, NB, NS |
| Symptoms of disseminated Lyme disease[1] | Yes/No | MB, ON, NB, NS |
| Symptoms of disseminated Lyme disease: Bell's palsy[1] | Yes/No | ON, NB, NS[1] |
| Symptoms of disseminated Lyme disease: other neurological symptoms[1,3] | Yes/No | ON, NB, NS[1] |
| Symptoms of disseminated Lyme disease: cardiac symptoms[1,4] | Yes/No | ON, NB, NS[1] |
| Symptoms of late Lyme disease: Recurrent arthritis/joint swelling[1] | Yes/No | ON, NB, NS[1] |
| Method of diagnosis[1] | Category: Serology/PCR/Culture | MB, ON, NB, NS* |

1 Data collected in the Lyme Disease Enhanced Surveillance system are indicated by an asterisk, otherwise data were collected via the National Notifiable Disease Surveillance System.

2 Forward Sortation Area of residence was considered the location of acquisition in the absence of recorded travel or exposure history to a known Lyme disease risk area in Canada or abroad.

3.Radiculoneuropathy, encephalitis, lymphocytic meningitis, and encephalomyelitis.

4.Atrioventricular heart block and myocarditis

5 PEI provided Lyme Disease Enhanced Surveillance data elements for 2012 in August 2014; therefore this information was not included in this analysis.

Abbreviations: AB: Alberta, SK: Saskatchewan, MB: Manitoba, ON: Ontario, NB: New Brunswick, NS: Nova Scotia, PEI: Prince Edward Island, NL: Newfoundland and Labrador

# Review of methods to prevent and reduce the risk of Lyme disease

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## Abstract

**Background:** Cases of Lyme disease and areas with self-sustaining populations of vector ticks are increasing in Canada. This trend is expected to continue. Preventing Lyme disease will therefore become relevant to an increasing number of Canadians.

**Objective:** To summarize methods for reducing the risk of tick bites and preventing transmission once a tick is feeding.

**Methods:** A literature search was conducted to identify methods to reduce the risk of tick bites and the abundance of vector ticks, as well as the risk of becoming infected with the Lyme disease pathogen, *Borrelia burgdorferi* (BB), if bitten by a vector tick.

**Results:** Current approaches to reducing the risk of tick bites or preventing infection with BB once bitten are largely reliant on the individual. They include use of topical repellents, use of protective clothing, avoidance of risk areas and removing ticks soon (ideally within a day) after they attach. These methods are efficacious, but constrained by user adherence. Other approaches such as landscape modification or the use of acaricides to control ticks, have shown promise in other countries, but have not been widely adopted in Canada.

**Conclusion:** Lyme disease will continue to present a threat in Canada. In additional to the existing interventions for prevention of tick bites and Lyme disease, there is a need for new tools to help reduce the risk of Lyme disease to Canadians.

## Introduction

Lyme disease is a serious human illness caused by the bacterium *Borrelia burgdorferi* (BB). It is transmitted by certain species of *Ixodes* ticks: the western blacklegged tick (*Ixodes pacificus*) in some areas west of the Rocky Mountains and the blacklegged tick (*Ixodes scapularis*) in parts of Canada east of the Rockies. These ticks are infected when they feed on BB-infected wild animal hosts such as rodents and birds. Once infected, they can transmit BB to other animals including humans (1).

Risk of contracting Lyme disease in Canada is highest where populations of blacklegged ticks are established (i.e., when populations are self-sustaining from year to year) (2). Tick occurrence and risk varies on either side of the Rockies. *Ixodes pacificus* populations are widely established in southern BC. They do not show evidence of expansion and usually have a low BB infection rate (<5%). As a result, risk is relatively modest. In contrast, the geographic range of established populations of *I. scapularis* (east of the Rockies) has recently expanded into central and eastern Canada (2, 3) and now includes areas near or within urban centers (4,5). Moreover, the proportion of *I. scapularis* infected with BB can be high (>15%). The combined effect for some affected areas are more infected ticks, closer to population centers and hence a relatively increased risk for Lyme disease in central and eastern Canada.

The annual incidence of reported Lyme disease cases has increased markedly in Canada. For example, in 2004 there were only 40 reported cases, however by 2012, there were 338 reported cases (2). Given that the vector range expansion trend is predicted to continue (2, 4), the need for effective interventions to prevent tick bites and Lyme disease is becoming increasingly important.

Unfortunately, there are relatively few options available for Canadians to prevent Lyme disease. There is no vaccine for human use (however, there are effective treatments for Lyme disease); tick-killing acaricides are not widely available or used (6); and professional expertise/infrastructure for tick management is limited. Consequently, prevention relies on measures undertaken by the individual – usually by preventing bites and/or by removing attached ticks before transmission of BB occurs (7, 8, 9, 10, 11). The purpose of this review is to summarize the methods that individuals can use to prevent and manage tick bites to prevent or reduce the risk of Lyme disease. Emphasis is on approaches targeting *I. scapularis*, but recommendations are generally applicable to *I.pacificus* and other tick species.

## Methods

A literature search was conducted focussing on measures used to prevent and/or control ticks and their bites. Open source databases (e.g., PubMed, The United States Armed Forces Pest Management Board Literature Retrieval System (http://www.afpmb.org/content/welcome-literature-retrieval-system) were searched for relevant publications using the search terms: "tick" and "repellent"; "Lyme disease" and "prevention"; or, "*Ixodes scapularis*" and "control". Studies, reviews or reports of interventions or measures were reviewed that had evidence of efficacy, were adopted in other countries and had biologic plausibility that they would reduce risk. The findings were summarized in a narrative review and used to develop the following guidance and recommendations on Lyme disease prevention for Canadians.

## Results

Reports were summarized regarding four prevention methods: avoidance of risk areas; use of protective clothing and prompt tick removal; use of chemical barriers/repellents; and reducing tick abundance in the environment.

### 1. Prevent Lyme disease by avoiding areas of risk

A simple rule for Lyme disease is: if you don't get 'ticked', you don't get sick. Until recently, at least in Canada, this could be achieved by avoiding the few areas where Lyme disease occurred (12, 13). However, with the spread of *I. scapularis* and Lyme disease, vector ticks can be found in many more areas including near to and within densely populated centers and even on residential properties (3). Nevertheless, avoidance remains a viable risk-reduction approach (10).

Ticks are associated with specific habitats (14,15) particularly in and around woodland areas (**Figure 1**) that support populations of rodents, birds and deer which are the main hosts for blacklegged ticks (16). In such areas, ticks are often found in leaf litter at edges (ecotone) of forested habitats, which include hiking or animal trails (16). Indeed, they can thrive in small patches of woodland, including those found in backyards, but are rarely found on lawns, especially those kept short (17,18,19). Thus, if woodland and ecotonal habitats can be avoided, the risk of tick bites is generally very low (20). Conversely, visiting such habitats increases exposure and should prompt consideration of use of additional protective measures, such as repellents (Section 2 below).

**Figure 1: Typical habitat that would support blacklegged tick populations and where blacklegged ticks might be encountered**

Ticks are associated with specific geographic regions and risk of tick bites and Lyme disease is highest in areas where tick populations are established and self-sustaining. Tick bites and Lyme disease can however, occur in areas where established tick populations are unknown, either because surveillance has yet to identify the population, or because small numbers of 'adventitious' ticks (ticks spread out of established populations by migrating birds) are present (2,3,13,21). Thus, avoiding areas where tick populations are known to be established will reduce but may not eliminate risk.

Risk of Lyme disease also varies with the stage of the tick and by season. Larval ticks (youngest stage) may occasionally bite people but, as they are not infected with BB (22), they are not a threat for Lyme disease although they can occasionally be infected with other pathogens. In Canada, risk is highest in the spring and summer (May through August) when nymphs (the juvenile stage of ticks that have developed from fed larvae preceding adulthood) are active (23, 24). The increased risk associated with nymphs likely represents their relatively higher abundance (compared to adults), as well as our reduced efficiency at finding and removing this smaller life stage before transmission occurs (25). Risk also exists earlier in the spring as well as into the autumn when adult ticks are most active (26) and theoretically in the winter if temperatures are above freezing and snow is not on the ground (16,27). Using personal protective measures or avoiding risk areas during the times of year that nymphal and adult ticks are active will significantly reduce or eliminate exposure (28).

## 2. Prevent Lyme disease by dressing appropriately and by removing attached ticks

Individuals who work outdoors or participate in outdoor activities such as golfing, hunting, camping, fishing and hiking may not be able to avoid tick habitats, but they can reduce their risk of contracting Lyme disease. Interventions include dressing appropriately and the removal of attached ticks as soon as possible.

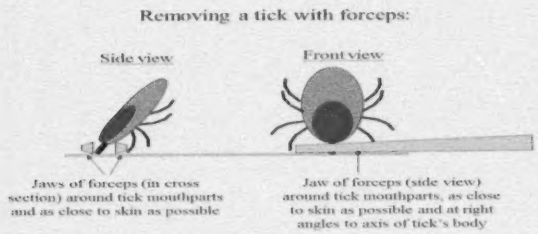
Blacklegged ticks typically wait for a passing host in leaf litter or on vegetation such as low shrubs. From this perch, they grasp onto hosts as they pass and then crawl around to find a place to feed (16, 29). Wearing appropriate clothing such as closed-toe shoes, long shirts tucked into trousers and socks pulled over pant legs, limits access to skin, thereby protecting against bites (30). Further, tucked in clothing forces the ticks to travel longer distances on outer garments to find open skin, which should increase the probability that they will be seen and removed before they feed. Wearing light coloured clothing also makes it easier to notice and find ticks (31). To kill any ticks that remain on clothing after use, put garments through a high heat dry cycle if possible (32), then wash and dry again.

Vector ticks feed on their human hosts for up to seven days (16). It has been well established in animal models that most cases of BB transmission does not occur until a day or more after ticks begin to feed (33,34,35). Therefore, removal of ticks within 24 to 36 hours should prevent infection with *B. burgdorferi* in most cases. Indeed, there is evidence that daily checks of one's body for ticks and bathing/showering within a few hours after

outdoor activity (which increases the chances of finding ticks) reduces the risk of Lyme disease (36). Usually, a tick check should be done after leaving a risk area, although it is also prudent to check for ticks that might be moving over clothing or skin while in tick habitats.

Removal is best done with medium-tipped, stiff and angled forceps (tweezers) placed around the head of the tick as near as possible to the skin, followed by an upward pulling movement (34,37,38,39) as shown in **Figure 2**. After the tick is removed, the bite site should be cleaned with soap and water and/or treated with an antiseptic.

**Figure 2: Diagram depicting the preferred method for removal of attached ticks**


Removing a tick with forceps:
Side view
Front view
Jaws of forceps (in cross section) around tick mouthparts and as close to skin as possible
Jaw of forceps (side view) around tick mouthparts, as close to skin as possible and at right angles to axis of tick's body

## Prevent Lyme disease by using chemical barriers

Topical repellents can prevent the bites of a wide variety of insect vectors, including ticks (40, 41). In Canada, the most widely available repellent is N,N-diethyl-m-toluamide (DEET). It protects against tick bites, has been reviewed for safety by Health Canada and is a preferred active ingredient for protection against a range of other insect-transmitted pathogens (40, 42, 43). Generally, products that contain higher concentrations of DEET (e.g., 20 to 30%) provide longer periods of protection (44).

These higher concentration products are registered for use on adults and children over the age of 12. Children between the ages of two and 12 can use products that contain up to 10% DEET, but no more than three times daily. For children aged from six to 24 months, concentrations of up to 10% DEET can be used, but only once per day (44, 45).

Recently, repellents containing an ingredient called Icaridin, which provides levels and periods of protection similar to DEET, have become available in Canada (46). Icaridin (also called Picaridin and KBR 3023) has been used in other countries for some time, is recommended for protection against the bites of ticks (40, 43) and, in contrast to DEET, use of higher concentrations (e.g., 20%) is not limited by age (http://publications.gc.ca/collections/collection_2011/sc-hc/H113-9-2011-10-eng.pdf). Thus, if longer protection periods are needed for children, Icaridin might be the preferred repellent. At the time of writing, Icaridin-containing products were not widely available in retail outlets in Canada. However, several companies are planning to market products (including those that contain 20% Icaridin) across the country in the near future (i.e., spring/summer 2015). For all topical repellents, it is important to read and follow all label directions.

Other insecticides such as permethrin,when impregnated into clothing, also act as a personal protective measure against tick bites (47,48). A recent randomized control trial (RCT) study of persons at high risk of tick exposure demonstrated substantial protection (>90%) compared to subjects using standard tick bite prevention measures (49).

Permethrin is not currently available to the general public in Canada but it is recommended that Canadians travelling to highly endemic areas of the US (40) and elsewhere (e.g., in Europe) apply permethrin treatments to their clothing or use clothing pre-treated with permethrin. These products can often be obtained in some travel clinics or from outdoors retailers when in the US (40).

Products that contain permethrin or other active ingredients that are not specifically approved for treatment of clothing to prevent tick bites must not be used for this purpose, as they have not been designed for such use. They may not work and/or pose a health risk if so used.

### 3. Prevent Lyme disease by reducing the number of ticks in the environment

Approaches such as landscape design and management or pesticide application have shown some success in reducing contact between ticks and people in the US and may have a role in Canada.

Simple landscape modifications such as thinning trees and shrubs can reduce an area's suitability for ticks. Tick 'unfriendly' zones can also be created around yards and leisure areas by integrating landscape structures (e.g., a raised deck) and management practices (e.g., grass cutting and scrub removal) (50). For people living in areas where ticks occur, fencing (eight to ten feet high) to keep the deer off their properties reduces Lyme disease risk (36).

Pesticides applied on vegetation in areas where ticks occur, such as in transition areas between woodlands and lawns, can substantially reduce tick populations (9, 51, 52). This approach has not been widely used in Canada, perhaps because Lyme disease is a 'new' problem and a market has not yet developed. Alternatively, it might reflect concern about pesticide safety or cost (53). Moving forward, individuals, organizations and municipalities will need to balance the use of pesticides to control ticks against cost, benefit and existing and future regulations and legislation related to pesticide application.

Treatment of deer (the main hosts for adult ticks) and rodents (the main reservoirs of the pathogen that carry Lyme disease) with acaricides to kill ticks have shown efficacy in proof-of–principle studies (54, 55). However, there is little evidence that deer culls are effective in reducing tick abundance except in unique environmental settings such as on islands (56).

## Conclusion

Over the last few years, Lyme disease in Canada has evolved from an unusual and focal issue, to an emergent and expanding problem. Increasingly, ticks and hence the risk of Lyme disease is encroaching into populated areas. This trend is expected to continue, and as a result, more Canadians will be at increased risk of exposure to tick bites and Lyme disease. Apart from landscape modification to reduce environmental risk, tools to prevent bites and BB infection are largely limited to personal approaches such as the use of repellents and tick checks. While evidence supports the effectiveness of these interventions (although assessment of the degree of effect and quality of evidence awaits systematic reviews), effectiveness is constrained by low levels of adherence (57, 58, 59). Continued efforts to inform Canadians about the risk of Lyme disease and to encourage them to protect themselves against bites and disease are warranted. However, new tools and approaches are also needed, in particular those that complement existing strategies. These may include novel approaches that encourage the use of existing methods and enhance public adherence to recommended personal protection methods; broader use of existing and/or novel methods to control ticks (or BB in ticks and animal reservoirs); development and use of efficacious and publically-acceptable human vaccines; and continuous improvements to risk assessment and forecasting tools.

### Summary of recommendations

| Strategy/Method | Rationale for use | Selected References |
|---|---|---|
| Use approved and topical repellents (DEET or Icaridin) on skin (follow label directions) and wear insecticide-treated clothing (where permitted). | Prevents ticks from biting; some products can kill ticks. | (40, 42, 60) |
| Perform tick checks at least once a day and remove any ticks that are found. | Removes tick before transmission of the Lyme disease pathogen can occur. | (38, 61) |
| Avoid tick infested habitats. | Prevents exposure to ticks. | (10, 62) |
| Bath or shower within 2 hours after leaving tick habitat. | May dislodge unattached ticks and provides additional opportunity to find/remove attached ticks. | (36) |
| Wear appropriate clothing, e.g., light-coloured and long sleeve shirts, socks and full trousers. | Limits or delays access by ticks to sites for attachment and improves ability to detect (and remove) unattached ticks on clothing. | (30) |
| Modify yards to reduce tick-bite risk: Fence yards (8+ feet high), thin trees and shrubs in play areas, create 'tick unfriendly' zones at the edges of play areas. | Reduces entry of tick hosts into yards and reduces number of ticks in play areas by reducing their survival. | (36, 50) |

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## Conflict of interest

None

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## ID News: Zika virus in Brazil

International Society for Infectious Disease ProMED-mail post. **Zika virus – Brazil: Confirmed May 15, 2015** Posted May 19, 2015 (Summary)

The Ministry of Health in Brazil has announced that Zika virus is circulating in Brazil. The majority of cases are asymptomatic. Those who develop symptoms typically present with low grade fever, conjunctivitis, arthralgias, myalgias and a macular-papular rash. The incubation period is approximately 4 days and signs and symptoms can last for 7 days. No mortality is associated with the infection. The virus is transmitted by bite of *Aedes aegypti* mosquito that also transmits dengue and chikungunya viruses.
Treatment is symptomatic. The use of salicylic acid [aspirin] and anti-inflammatory drugs is contraindicated due to the risk of hemorrhagic complications. It is important for health professionals to remain alert to this possibility when dealing with suspected dengue cases.